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EXAMINER	
SGAGIAS, MAGDALINE K	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/531,366	HOLM, PER SONNE	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *21 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *150-177 and 179-196* is/are pending in the application.

4a) Of the above claim(s) *150-177* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *179-196* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 01/21/2010 have been fully considered. Claims 150-177, 179-196 are pending. The amendment has been entered. Claims 1-149, 178 are canceled. Claims 150-177 are withdrawn. Claims 179-196 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 184 is withdrawn in view of the amendment.

The rejection of claim 185 is withdrawn in view of the amendment.

Claim Objections

Claim**195** is objected to because of the following informalities: Second line recites the term replicationdeficient. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims **179-193, 195-196** under 35 U.S.C. 103(a) as being unpatentable over by **Steegenga et al,** (Oncogene, 16: 349-357, 1998 (IDS) in view of **Holm et al** (JBC

277(12): 10427-10434, Published, JBC Papers in Press, January 11, 2002 (IDS); **Steenenga et al,** (Molecular and Cellular Biology, 19(5): 3885-3894, 1999) is withdrawn in view of the declaration.

The rejection of Claim **194** under 35 U.S.C. 103(a) as being unpatentable over by Steegenga et al, (Oncogene, 16: 349-357, 1998 (IDS) in view of Holm et al (JBC 277(12): 10427-10434, Published, JBC Papers in Press, January 11, 2002 (IDS); Steenenga et al, (Molecular and Cellular Biology, 19(5): 3885-3894, 1999) and further in view **of Li et al,** (Cancer Research, 61: 6428-6436, 2001) is withdrawn in view of the declaration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims **179, 181, 183, 187, 195** are rejected under 35 U.S.C. 102(b) as being anticipated by **Steegenga et al,** (Oncogene, 16: 349-357, 1998 (IDS).

Steegenga et al, teach a recombinant adenovirus, wherein infection into Hep3B cells with the adenovirus that expresses a first polypeptide comprising E1B and E4orf6 and the second E1A polypeptide (figure 6, page 354) **(claims 179, 181, 183, 187).** Steegenga teaches apart from the large E1B protein the adenovirus early region encodes the E1A and E4orf6 proteins which have been reported to affect p53 expression as well as its functioning (abstract). After infection with wild-type adenovirus we observed a dramatic decrease in wild-type p53 expression while no down-regulation of p53 could be detected after infection with the ΔE1B virus (abstract). Steegenga et al, teach the different effects of the wild-type adenovirus and ΔE1B adenovirus on p53 expression were not only found in cells expressing wild-type p53 but

were also observed when tumor cells expressing highly stabilized mutant p53 were infected with these two viruses (abstract) **(claim 195).** Infection with different adenovirus mutants indicated the importance of a direct interaction between p53 and the large E1B protein for reduced p53 expression after infection. Moreover, coexpression of the E4orf6 protein was found to be required for this phenomenon, while expression of E1A is dispensable. In addition, Steegenga et al, teach that p53 is actively degraded in wild-type adenovirus-infected cells but not in ΔE1B - infected cells.

Thus, Steegenga et al, anticipates the claimed invention.

Claim Rejections - 35 USC § 103/Necessitated by Amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 179, **180,** 181, 183, 187, 195 are rejected under 35 U.S.C. 103(a) as being unpatentable over by **Steegenga et al,** [(Oncogene, 16: 349-357, 1998 (IDS) thereafter referred as Steegenga, 1998)] in view of **Fueyo et al** (20050260162).

Steegenga 1998, teach a recombinant adenovirus, wherein infection into Hep3B cells with the adenovirus that expresses a first polypeptide comprising E1B and E4orf6 and the second E1A polypeptide (figure 6, page 354) **(claims 179, 181, 183, 187).** Steegenga teaches apart from the large E1B protein the adenovirus early region encodes the E1A and E4orf6 proteins which have been reported to affect p53 expression as well as its functioning (abstract). After infection with wild-type adenovirus we observed a dramatic decrease in wild-type p53 expression while no down-regulation of p53 could be detected after infection with the ΔE1B

virus (abstract). Steegenga et al, teach the different effects of the wild-type adenovirus and ΔE1B adenovirus on p53 expression were not only found in cells expressing wild-type p53 but were also observed when tumor cells expressing highly stabilized mutant p53 were infected with these two viruses (abstract) **(claim 195).** Infection with different adenovirus mutants indicated the importance of a direct interaction between p53 and the large E1B protein for reduced p53 expression after infection. Moreover, coexpression of the E4orf6 protein was found to be required for this phenomenon, while expression of E1A is dispensable. In addition, Steegenga et al, teach that p53 is actively degraded in wild-type adenovirus-infected cells but not in ΔE1B - infected cells.

However, Steegenga 1998 does not specifically teach utilizing the recombinant adenovirus wherein the E1B polypeptide is E1B55 Kd polypeptide, in order to infect a tumor cell.

However, prior to the time of the claimed invention, **Fueyo et al** teach an adenovirus with an altered E1A and/or E1B region, in particular a full or partial deletion of the E1B55 kD protein encoding nucleic acid sequence of adenovirus [0257]. Fueyo et al teach an E1A mutation (e.g., a delta24 mutation in E1A) may be used in combination with mutations in the E1B region of the same adenovirus, thus producing a double mutant adenovirus (e.g., CB001) [0080]. Fueyo teaches the E1B55 kD protein has been shown to bind to and inactivate p53 [0080]. Fueyo et al teach a replication-competent adenovirus comprising a mutation in a nucleic acid sequence encoding an E1A, E1B, or an E1A and E1B polypeptide, wherein the E1A polypeptide is unable to bind Rb and the E1B polypeptide is unable to bind p53 [0014]. Fueyo teaches in particular, an adenovirus with an altered E1A and/or E1B region, in particular a full or partial deletion of the E1B55 kD protein encoding nucleic acid sequence of adenovirus [0257].

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459

(1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Steegenga 1998, to include the E1B55 kD protein encoding nucleic acid sequence of adenovirus, such as that taught by Fueyo, for infecting tumor cells with a reasonable expectation of success. One of ordinary skill in art would have been motivated to utilizing the E1B55 kD protein encoding nucleic acid sequence of adenovirus, to infect tumor cells in order to detect the presence of cells with a defective Rb and/or p53 pathway as taught by Fueyo [0240]. This is further underscored by the teachings of Fueyo that sample of cells could be infected with the oncolytic adenovirus and after an incubation period, the number of cells exhibiting adenovirus replication can be quantified to determine the number of neoplastic cells in the sample. This may be useful to determine if the adenovirus would be effective in treating the

tumor from a patient from which a cell sample was taken. Other uses are to diagnose a neoplasm as having a defective Rb and/or p53 pathway and to evaluate tumor cell load following treatment [0239]. Alternate diagnostic uses and variations include an adenovirus with a Rb binding mutation in the E1A or an E1B55 kD-mutation and a reporter gene to score whether cells have been transformed by detecting reporter gene expression [0241]. Expression of the reporter gene can be correlated with a phenotype of adenoviral replication indicating a lack of a functional Rb and/or p53 pathway [0241].

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 179, 181, **182,** 183, 187, 195 are rejected under 35 U.S.C. 103(a) as being unpatentable over by **Steegenga et al,** [(Oncogene, 16: 349-357, 1998 (IDS) thereafter referred as Steegenga, 1998)] in view of **Steenenga et al,** [(Molecular and Cellular Biology, 19(5): 3885-3894, 1999 (previously cited) thereafter referred as Steegenga, 1999)].

Steegenga 1998, teach a recombinant adenovirus, wherein infection into Hep3B cells with the adenovirus that expresses a first polypeptide comprising E1B and E4orf6 and the second E1A polypeptide (figure 6, page 354) **(claims 179, 181, 183, 187).** Steegenga 1998 teaches apart from the large E1B protein the adenovirus early region encodes the E1A and E4orf6 proteins which have been reported to affect p53 expression as well as its functioning (abstract). After infection with wild-type adenovirus we observed a dramatic decrease in wild-type p53 expression while no down-regulation of p53 could be detected after infection with the ΔE1B virus (abstract). Steegenga 1998, teach the different effects of the wild-type adenovirus and ΔE1B adenovirus on p53 expression were not only found in cells expressing wild-type p53 but were also observed when tumor cells expressing highly stabilized mutant p53 were infected with these two viruses (abstract) **(claim 195).** Infection with different adenovirus mutants

indicated the importance of a direct interaction between p53 and the large E1B protein for reduced p53 expression after infection. Moreover, coexpression of the E4orf6 protein was found to be required for this phenomenon, while expression of E1A is dispensable. In addition, Steegenga 1998, teach that p53 is actively degraded in wild-type adenovirus-infected cells but not in ΔE1B -infected cells.

However, Steegenga 1998 does not specifically teach utilizing the recombinant adenovirus wherein the E1A polypeptide is E1A12S polypeptide, in order to infect a tumor cell.

However, prior to the time of the claimed invention, Steegenga, 1999 teach that there is a distinct regulation of p53 and p73 activity by adenovirus E1A, E1B, E4orf6 and E1A12S proteins (p 3886-3892). Steegenga 1999 suggest in the early phase of Ad infection, when those early proteins are expressed, distinct AdE proteins are involved in inhibition of the transcription activation by both p53 and p73, although an effect on p73 activity during Ad infection has not been proven directly (p 3893, 2nd column 5th paragraph). Steegenga 1999 conclude that the E1A proteins including E1A12S seem to have a similar effect on p53 and on p73, but these proteins are differently affected by the large E1B and E4orf6 proteins (p 3894, 1st column). However, the final effect is that both the p53 and the p73 proteins are functionally inactivated as a result of both infection and transformation by Ad (p 3894, 1st column). Apart from the p73 gene, the p53 family contains at least one other member: the KET/p51/p40/p63 protein and it will be interesting to investigate whether the different forms of this p53 homologue can be inactivated by the AdE proteins as well (p 3894, 1st column).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary

rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Steegenga 1998 to include the E1A12S polypeptide, such as that taught by Steegenga, 1999, in transfecting a tumor cell with a reasonable expectation of success. One of ordinary skill in art would have been motivated to utilize the E1A12S polypeptide in the adenovirus of Steegenga 1998 since Steegenga, 1999, suggest it would be interesting to investigate whether the different forms of the p53 homologue can be inactivated by the AdE proteins as well including E1A12S polypeptide (p 3894, 1st column).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 179, 181, 182, **183-196** are rejected under 35 U.S.C. 103(a) as being unpatentable over by Steegenga et al, [(Oncogene, 16: 349-357, 1998 (IDS) thereafter referred as Steegenga, 1998)] in view of Steenenga et al, [(Molecular and Cellular Biology, 19(5): 3885-

3894, 1999 (previously cited) thereafter referred as Steegenga, 1999)] and further in view of **Irving et al** (20030095989); **of Li et al,** (Cancer Research, 61: 6428-6436, 2001 (previously cited)).

Steegenga 1998, teach a recombinant adenovirus, wherein infection into Hep3B cells with the adenovirus that expresses a first polypeptide comprising E1B and E4orf6 and the second E1A polypeptide (figure 6, page 354) **(claims 179, 181, 183, and 187).** Steegenga 1998 teaches apart from the large E1B protein the adenovirus early region encodes the E1A and E4orf6 proteins which have been reported to affect p53 expression as well as its functioning (abstract). After infection with wild-type adenovirus we observed a dramatic decrease in wild-type p53 expression while no down-regulation of p53 could be detected after infection with the ΔE1B virus (abstract). Steegenga 1998, teach the different effects of the wild-type adenovirus and ΔE1B adenovirus on p53 expression were not only found in cells expressing wild-type p53 but were also observed when tumor cells expressing highly stabilized mutant p53 were infected with these two viruses (abstract) **(claim 195).** Infection with different adenovirus mutants indicated the importance of a direct interaction between p53 and the large E1B protein for reduced p53 expression after infection. Moreover, coexpression of the E4orf6 protein was found to be required for this phenomenon, while expression of E1A is dispensable. In addition, Steegenga 1998, teach that p53 is actively degraded in wild-type adenovirus-infected cells but not in ΔE1B -infected cells.

However, Steegenga 1998 does not specifically teach utilizing the recombinant adenovirus wherein the E1A polypeptide is E1A12S polypeptide, in order to infect a tumor cell.

However, prior to the time of the claimed invention, Steegenga, 1999 teach that there is a distinct regulation of p53 and p73 activity by adenovirus E1A, E1B, E4orf6 and E1A12S proteins (p 3886-3892). Steegenga 1999 suggest in the early phase of Ad infection, when those

early proteins are expressed, distinct AdE proteins are involved in inhibition of the transcription activation by both p53 and p73, although an effect on p73 activity during Ad infection has not been proven directly (p 3893, 2nd column 5th paragraph). Steegenga 1999 conclude that the E1A proteins including E1A12S seem to have a similar effect on p53 and on p73, but these proteins are differently affected by the large E1B and E4orf6 proteins (p 3894, 1st column). However, the final effect is that both the p53 and the p73 proteins are functionally inactivated as a result of both infection and transformation by Ad (p 3894, 1st column). Apart from the p73 gene, the p53 family contains at least one other member: the KET/p51/p40/p63 protein and it will be interesting to investigate whether the different forms of this p53 homologue can be inactivated by the AdE proteins as well (p 3894, 1st column).

Steegenga, 1998 and Steegenga, 1999 do not specifically teach the first or second polynucleotide is operably linked to an YB-1-controlled promoter.

However, at the time of the instant invention **Irving et al** teach an adenovirus genome comprising YB-1 controlled promoters and lacking E1A [0013] **(claim 184).** As demonstrated from the text and figures, this virus comprises all other adenoviral genes except E1A and in some cases E3 (sees e.g. figure I and [0052]). Therefore, the vector comprises E1-B 55 Kda and E4orf6 and a promoter for each of these genes. Irving et al teach an adenovirus vector comprising YB-1 sequences and the vector is replicable [0028]. Irving teaches that adenovirus early genes, especially E1a, E1b, E2 and E4. E1a can be functionally replaced by a select group of transactivators also capable of promoting transcription of E1b, E2, and E4, which typically also modulate endogenous gene expression in the host cell [0052]. Since E1a is pleiotropic, the invention will be understood to include embodiments in which one of the functional sub elements of E1a is deleted or suppressed, and substituted with a heterologous gene [0052]. Similarly, E2 can be replaced by an encoding region for one or more proteins that

mimic the function of the E2 gene products: a single-stranded DNA binding protein, a DNA polymerase, and a terminal protein [0052]. Candidate transactivators to replace E1a include viral transactivator genes from other viruses, such as members of the herpes simplex virus family, and SV40 [0053]. Of particular interest are the immediate early genes from cytomegaloviruses (CMV) that are cytopathic for humans or other vertebrates--including the genes known as IE1 and IE2 (SEQ. ID NO:4) [0053]. Immediate early genes function to regulate viral and cellular gene expression during the course of CMV replication [0053]. The major IE region of the CMV genome is believed to activate viral genes and represses genes of the host cell [0053] **(claims 185-193).** Irving teaches the YB-1 interacts with proliferating cell nuclear antigen and may translocate to the nucleus by a protein kinase C mediated signal transduction pathway [0054] **(claim 196).**

However Steegenga (1998)/Steenenga (1999)/ **Irving et al** do not teach an IRES sequence, wherein the IRES sequence separates the nucleic acid sequences encoding the first and second polypeptides.

However, at the time of the instant invention **Li et al** teach an AFP-E1AIRES-E1B bicistronic expression cassette fulfilled the necessary requirements and created an AFP-producing hepatoma-specific adenovirus variant, CV890, for additional clinical development (p 6.428, 2nd column, 2nd paragraph). Li teaches a tumor-specific adenovirus by linking two essential viral genes, *E1A* and *E1B,* with an IRES . Use of an AFP TRE-E1A-IRES-E1B cassette yields a virus of very high specificity for target cells (5,000–100,000:1) with only a single tumor-specific transcriptional regulatory element (TRE) (p 6.428, 2nd column, 2nd paragraph). The TRE-E1A-IRES-E1B bicistronic cassette strategy saves space within the virus genome allowing the reincorporation of the adenovirus E3 region adding much needed antitumor efficacy in vivo and in vitro (p 6.428, 2nd column, 2nd paragraph).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Steegenga 1998/ Steegenga 1999 to include the adenovirus genome comprising YB-1 controlled promoter as taught by Irving and in addition, to include a tumor-specific adenovirus by linking two essential viral genes, *E1A* and *E1B,* with an IRES as taught by Li in order to transfect a tumor cell with a reasonable expectation of success. One of ordinary skill in art would have been motivated to include YB-1 controlled promoter since Irving suggests that vector particles deficient in the E1a gene can be produced in cells that express either a Y box protein such as YB-1, or a CMV immediate early gene such as IE1 or IE2 [0070] and the

replacing gene is put under control of a heterologous transcription control element that promotes transcription of the gene in the selected host cell in either a constitutive or inducible fashion or the replacement gene is inserted by heterologous recombination behind a promoter endogenous and active in the host cell or a vector is constructed in which the replacement gene is operatively linked to a promoter from another source--such as the SV40 promoter, or the promoter for phosphoglycerate kinase (PGK) the vector is then transfected into a suitable host cell, from which the genetically altered line is cloned [0071]. One of ordinary skill in art would have been motivated to include adenovirus E1A, E1B, E4orf6 and E1A12S proteins in the early phase of Ad infection, in the system since Li suggests an AFP-E1AIRES-E1B bicistronic expression cassette fulfilled the necessary requirements and created an AFP-producing hepatoma-specific adenovirus variant, CV890, for additional clinical development (p 6.428, 2nd column, 2nd paragraph). In addition, Li provide sufficient motivation for one of ordinary skill in the art to apply the IRES sequences to the sequences of Steegenga (1998)/Steenenga (1999) in order to target specific cells in vitro for the studying if there is a distinct regulation of p53 and p73 activity by adenovirus E1A, E1B, E4orf6 and E1A12S proteins in the early phase of Ad infection, when those early proteins are expressed, distinct AdE proteins are involved in inhibition of the transcription activation by both p53 and p73 as suggested by the teachings of Steegenga (1998)/Steenenga (1999).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Applicants arguments are not related to the instant rejection.

Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent

possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985); In re Van Omum, 686 F.2d 937,214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ'644 (CCPA 1969). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321 (d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of Claims 179-196 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 104-117 of copending Application No. 10/579,543 is withdrawn since the instant application is filed before the '543 application.

Claims 179-185, 187-191, 194-196 **remain** provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 47-51, 53, 59-60, 65 of copending Application No. 10/451,210. The instant claims recite the YB-1 sequence is under the control of a promoter while the '210 do not explicitly recite a promoter for this sequence. It would have been obvious for the ordinary skilled artisan to make a choice of between a first polypeptide comprising an E1B polypeptide, an E4 polypeptide or an E1B and E4 because expression of the E1B and E4 sequence is essential for operation of the adenoviral replication system recited in the '210 claims. The claims are therefore obvious one over the other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants request to hold the rejection in abeyance until there is allowable subject matter.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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